Remarks

Reconsideration of this Application is respectfully requested. Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 14-29 are pending in the application, with claim 14 being the independent claim. Claims 14-29 are hereby amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II Amendment

Claims 14-29 have been amended to more particularly point out what Applicant regards as the invention. Claim 14 and its dependent claims 15-29 have been amended to recite a needleless injection system comprising a needleless syringe, wherein the syringe comprises microparticles. Claim 14 has also been amended to replace the term, "such that," with the term, "wherein." Finally, the microparticles are specified to be delivered transdermally, transmucosally, or subcutaneously, or into the skin by the needleless syringe in claim 14. Support for the amendment to these claims can be found, *inter alia*, at page 2, lines 21-22; page 3, lines 11-14; page 10, lines 4-11, of the specification, and claim 10 as originally filed.

Claim 24 has been amended to specify that the therapeutic agent of the needleless injection system is a nucleic acid. Support for this amendment can be found, *inter alia*, at page 5, lines 14-16, of the specification.

Claim 25 has been amended to specify that the carbohydrate is trehalose. Support for this amendment can be found, *inter alia*, at page 8, lines 9-12, of the specification.

Claim 26 has been amended to recite that the microparticles of the needleless injection system are delivered into a patient's skin, or delivered through the skin by the needleless syringe. Support for this amendment can be found, *inter alia*, at page 1, lines 5-7 and page 10, lines 8-11, of the specification.

III. The Double Patenting Rejections

At pages 2-3 of the Office Action, the Examiner has issued a provisional double patenting rejection of claim 24 under 35 U.S.C. § 101 as claiming the same invention over claims 38, 40, and 42-53 of copending Application No. 10/902,464 (the '464 application). The Examiner also has issued a provisional nonstatutory obviousness-type double patenting rejection of claims 14-23 and 25-29 as claiming the patentably non-distinct invention over claims 38, 40, and 42-53 of the '464 application.

As presently amended, the therapeutic agent of the microparticles in a needleless injection system in claim 24 is not a vaccine. Rather, it is a nucleic acid. Further, claim 14 and its dependent claims 15-29 do not recite that the therapeutic agent is a vaccine. Such agent could encompass a wide variety of pharmacologically active substances, such

as local anesthetics or constructs for gene therapy and steroids. *See* page 5, line 14 to page 6, line 6, of the specification.

Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of these claims.

IV. The Rejection Under 35 U.S.C. § 103

At pages 3-6 of the Office Action, claims 14-29 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bellhouse *et al.* in view of U.S. Patent No. 5,707,644 to Illum *et al.* (the '644 patent). More specifically, the Examiner states that Bellhouse *et al.* disclose a needleless injector comprising microparticles comprising active agents for transdermal or transmucosal delivery. The '644 patent, according to the Examiner, discloses a micro-sphere formulation comprising a drug, stabilizing compounds (i.e. starch derivatives), polypeptides, and vaccines, and such formulation is delivered transmucosally via a nasal insufflator; the microspheres disclosed in the '644 patent also meet the size and shape limitation of the instant claims. Accordingly, the Examiner alleges that it would have been obvious to use the particle formulation of the '644 patent in the needleless injector of the Bellhouse article to deliver a stable powder formulation via a needleless injector. Applicant respectfully traverses the rejection for at least the following reasons.

First, the needleless syringe of the claimed needleless injection system is adapted to be pressed against a patient's skin for transdermal, transmucosal, subcutaneous delivery, and its operation involves injection into or through the skin using *needleless injection*. *See* page 1, lines 6-7 and lines 11-13; page 3, lines 12-14; and page 10, lines

8-11, of the specification. Both the needleless syringe and the microparticle properties can be used to control the depth of delivery of a therapeutic agent into the skin, preferably to the epidermis, where there is a large concentration of immune cells. Delivery to the epidermis may elicit a stronger cell mediated and humoral immune response. For example, the claimed needleless syringe can deliver nucleic acids *directly* to a cell to bypass the cell uptake.

The nasal insufflator disclosed in the '644 patent, on the contrary, does not deliver a composition subcutaneously, transmucosally, transdermally, or into or through the skin using needleless injection. A nasal insufflator produces material for deposition on a surface, not for injection. Therefore, it is not a needleless injector. *See, e.g.* WO 94/2463, page 1, line 30 to page 2, line 2, for the definition of a needleless injector (as disclosed in page 5, line 8, of the specification). More specifically, according to the '644 patent, a composition is deposited on the nasal mucosa and then absorbed across the mucosa following deposition. *See* column 6, lines 39-40; column 6, lines 44-45, and column 8, line 64 to column 9, line 3. Thus, cell uptake is required. Further, a nasal insufflator does not have the ability to deliver particles transmucosally, since the speed of delivery of the microparticles from an insufflator will not be sufficient to penetrate the mucosa. This is evident from the deposition of the composition on the mucosa. *See* '644 patent, column 8, line 52. The bioadhesive microspheres (diameter of 0.1 μm to 10 μm) disclosed in the '644 patent adhere to the nasal mucosa. *See* column 2, lines 22-31. Preferably, the microspheres of the '644 patent gel on contact with the mucosal surface. *See* column 3, lines 26-28.

Accordingly, the '644 patent actually teaches away from using transmucosal delivery, since such adhesion would not be necessary if the microspheres were delivered transmucosally. In addition, the '644 patent does not teach subcutaneous delivery, because this form of delivery is used as a comparison with the delivery by absorption of the mucosal surface. *See* column 12, lines 2-4 and line 60.

Second, as presently amended, the needleless injection system in the claimed invention comprises microparticles which are specifically adapted for needleless injection, i.e., the microparticles are in a needleless syringe. These specified microparticles have a relative particle density of *at least 80%* and comprise a therapeutic agent, a carbohydrate or other glass-forming substance, *and a higher density additive* (which could be a metal carrier, for example, gold). The high relative particle densities are required to give mechanical strength for needleless injection system. *See* specification at page 5, lines 2-9. The unique feature of the higher density additive provides improved transmucosal delivery of the microparticles, requires lower particle velocity, and may reduce the possibility of damage to the skin. The higher density additive also provides the advantage of improved penetration. *See* **EXHIBIT A**, page 1524 of Lahm *et al.*, J. Pharm. Sci. 95:1511-1526 (2006).

In contrast, Bellhouse *et al.* neither teach nor suggest the use of a higher density additive in combination with an active agent for needleless injection. (hydrophobic testosterone or hydrophilic lignocaine hydrochloride, *see* item 7 bridging pages 55 and 56 of Bellhouse *et al.*). Further, as admitted by the Examiner on page 4 of the Office Action, the particles of the needleless injector are silent to a glass-forming polymer, which is a feature of the claimed invention. Thus, Bellhouse *et al.* actually teach away

from using the microparticles of the claimed needleless injection system. The deficiencies of Bellhouse *et al.* are not cured by the '644 patent.

The microspheres disclosed in the '644 patent do *not* comprise a higher density additive and are not specifically adapted for needleless injection. The density, as referred by the Examiner at column 9, line 8 of the '644 patent, is in relation to the definition of aerodynamic diameter. Such density is irrelevant to the actual particles, because no units are specified. Furthermore, all of the particles demonstrated as being suitable for intranasal delivery of the microspheres by a nasal insufflator are prepared in a freeze-dried solid form (i.e. lyophilized form). *See* column 8, lines 32-35; column 9, line 56; column 10, lines 22 to 39; column 10, line 44; column 10, line 49; and column 12, line 45. No other form is suggested for delivery in the '644 patent. Such low density microspheres produced by conventional lyophilization are *not* suitable in the claimed needleless injection system:

> [t]he **low-density particulate** solids produced by **lyophilization** and spray-drying techniques are ideal for redissolution for parenteral administration in solution via syringe or catheters. However, **such particles are not useful for delivery from a needleless syringe in a solid form** . . . the preparations [need to be] . . . **densified** to provide particles . . . that are much better suited for delivery using a **needleless syringe**....

See page 20, lines 1-9, WO 98/10750 (**EXHIBIT B**), emphasis added. Accordingly, one skilled in the art would not have considered the particles disclosed in the '644 patent to be suitable for needleless injection, because these particles prepared by conventional lyophilization are not dense enough for needleless injection.

Thus, in the absence of any high relative particle density and higher density additives, the '644 patent does not teach or suggest microparticles for needleless injection, as claimed in the present invention.

Accordingly, Bellhouse *et al.* neither teach nor suggest the required features of the microparticles in the claimed needleless injection system, such as a higher density additive and a glass forming polymer. The deficiencies of Bellhouse *et al.* are not cured by the '644 patent. The advantage provided by a higher density additive for needleless injection is also not disclosed or suggested in the '644 patent, and the nasal insufflator does not deliver a composition subcutaneously, transdermally, transmucosally, or into or through the skin using needleless injection. One having ordinary skill in the art would not be motivated to modify the formulation of Bellhouse *et al.* in view of the '644 patent to make a stable powder formulation for transmucosal delivery via a needleless injection system. Nor would one having ordinary skill in the art have a reasonable expectation of success that the claimed invention would be produced.

Applicant therefore respectfully requests that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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